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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/051,013	10/09/1998	TIMOTHY H. BESTOR	48075-B-PCT	7512

7590 09/16/2005

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 09/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/051,013	BESTOR, TIMOTHY H.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 March 1998* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/22/2005 has been entered.

[2] The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

[3] Claims 48-56 are pending in the application.

[4] Applicant's amendments to the claims, filed on 3/22/2005 and 7/19/2005, are acknowledged. The claim listing filed on 3/22/2005 fails to satisfy the requirements of the revised amendment practice according to 37 CFR 1.121 for the reasons stated in the Office communication mailed on 6/15/2005. The claim listing filed on 7/19/2005 replaces all prior versions and listings of the claims.

[5] Applicant's arguments filed on 3/22/2005 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[6] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim to Domestic Priority

[7] Applicant's claim to domestic priority under 35 U.S.C. § 119(e) to provisional application 60/004,445, filed on 9/28/1995, is acknowledged. Applicant's claim to domestic priority under 35 U.S.C. § 120 to non-provisional application 08/594,866, filed on 1/31/1996, now abandoned, is acknowledged.

Claim Rejections - 35 USC § 112, Second Paragraph

[8] Claims 48-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 48, 49 (claim(s) 56 dependent therefrom), 50-52, 53 (claim(s) 56 dependent therefrom), and 54-55 are indefinite in the recitation of "LexA binding region" (claims 48-51) and "Lac operator sequence" (claims 52-55) as it is unclear from the claims and the specification as to applicant's intended nucleotide sequence of a LexA binding region or a Lac operator sequence. It is suggested that applicants clarify the meaning of "LexA binding region" and "Lac operator sequence."

Claim Rejections - 35 USC § 112, First Paragraph

[9] Claims 49-51 and 53-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 49 (claim(s) 50-51 and 56 dependent therefrom) and 53 (claim(s) 54-56 dependent therefrom) recite "vector comprising *cDNA*" (italics added for emphasis). This limitation was added in the claim amendment filed on 6/21/2004. MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description". In the remarks corresponding to that amendment, applicant failed to show support for a *cDNA* encoding a chimeric protein as recited in claims 49 and 53. A cDNA is obtained by reverse transcription of an mRNA and the examiner can find no explicit support for a cDNA encoding the chimeric protein and there is no disclosure of a reverse transcription reaction to obtain a cDNA encoding the recited chimeric protein. Further, based on the disclosure of the specification, it does not appear that applicant intends for the claimed vector to be limited to comprising cDNA (obtained by reverse transcription of an mRNA) encoding the chimeric protein. It is suggested that applicants replace "cDNA" with, for example, "DNA."

[10] The written description rejection of claims 48-56 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below.

RESPONSE TO ARGUMENT: Applicants argue: 1) the genus of chimeric proteins encompasses those comprising a wild-type *Spiroplasma* DNA methyltransferase polypeptide and is not limited to those comprising mutant *Spiroplasma* DNA methyltransferase polypeptides and 2) the specification discloses a representative number of species of the claimed genus of chimeric proteins and encoding nucleic acids.

Applicants' argument is not found persuasive. In response to argument 1), in accordance with MPEP 2111, the examiner has not narrowly interpreted the "*Spiroplasma* DNA methyltransferase" as encompassing only mutant forms of a *Spiroplasma* DNA methyltransferase polypeptide. Instead, in view of the definition of "DNA methyltransferase" as provided in the specification at p. 13, lines 3-11, the examiner has interpreted *Spiroplasma* DNA methyltransferase polypeptide as encompassing mutant *and* non-mutant sequences that are capable of specifically methylating CpG sites. Also, it is noted that the examiner has broadly interpreted LexA DNA binding protein in accordance with the specification (p. 15, lines 1-3), which states that the LexA DNA binding protein can be a mutant LexA DNA binding protein. Furthermore, although not expressly stated, the examiner has interpreted LacI protein as encompassing mutant LacI proteins.

In response to argument 2), there is no dispute that the specification discloses vectors encoding a non-mutant *Spiroplasma* DNA methyltransferase polypeptide fused

to a LexA binding protein or a LacI protein, *i.e.,* vector pLS (LexA-*Spiroplasma* DNA methyltransferase fusion) and pLM9 (LacI-*Spiroplasma* DNA methyltransferase fusion). See particularly Figures 11A and 12. The experimental results suggest that a LexA-*Spiroplasma* DNA methyltransferase fusion and a LacI-*Spiroplasma* DNA methyltransferase fusion are able to methylate CpG sites adjacent to their respective binding regions (Examples 6 and 7). However, there is no evidence that this methylation is *specific*, *i.e.,* there is no evidence that would suggest that the chimeric proteins comprising a non-mutant *Spiroplasma* DNA methyltransferase cannot methylate other CpG sites present in a DNA sequence, and in view of the teachings of the specification, one of skill in the art would not expect chimeric proteins comprising a non-mutant *Spiroplasma* DNA methyltransferase to have the ability to *specifically* methylate CpG sites adjacent to a LexA binding region or a LacI operator sequence. The claims are drawn to a genus of chimeric proteins that "specifically methylates CpG sites" adjacent to either a LexA binding region or a Lac operator sequence. The specification defines "specifically methylate" to mean "to bond a methyl group to a methylation site in a DNA sequence, which methylation site may be –CpG-, wherein the methylation is restricted to particular methylation site(s) and the methylation is not random" (p. 14, lines 28-32). According to the specification (p. 39, lines 13-24 and p. 40, lines 1-8),

> "the M.SssI moiety retains intrinsic activity towards all CpG sites and substantial methylation of collateral sites is to be expected; such indiscriminate methylation is lethal to mammalian cells. It is therefore necessary to make the DNA methyltransferase moiety dependent on LexA-mediated DNA binding; this may be accomplished by selection of mutant versions of M.sssI that have reduded intrinsic DNA binding activity...As mentioned above, the initial construct methylates both specific (that is, the SmaI target site) and non-specific CpG sites elsewhere on the plasmid. It is therefore necessary to transfer DNA binding authority from the catalytic moiety to the DNA binding moiety; this is done by selecting for mutations that prevent the methylation of non-specific sites while allowing methylation of the specific site."

According to applicant's specification, it would appear that in order for the chimeric polypeptide to function as recited in the claims, *i.e.,* the *Spiroplasma* DNA methyltransferase polypeptide specifically methylates CpG sites adjacent to a LexA binding region or a Lac operator sequence, it is necessary to mutate the *Spiroplasma* DNA methyltransferase in order to reduce its intrinsic DNA binding activity. As such, based on applicant's specification, it would appear that mutation of the *Spiroplasma* DNA methyltransferase polypeptide is necessary in order that the chimeric protein "specifically methylates CpG sites" adjacent to a LexA binding region or a Lac operator sequence.

In view of this disclosure, a skilled artisan would recognize that a chimeric protein comprising a non-mutant *Spiroplasma* DNA methyltransferase polypeptide would not be encompassed by the genus of claimed chimeric proteins because such a chimeric protein would not have the ability to *specifically* methylate CpG sites adjacent to a LexA binding region or a LacI operator sequence. As such, the examiner maintains that the specification fails to disclose even a single representative species of the claimed genus of chimeric proteins that *specifically* methylates CpG sites adjacent to either of a LexA and encoding nucleic acids. Given the lack of description of a representative number of chimeric polypeptides and encoding polynucleotides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[11] The enablement rejection of claims 48-56 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below.

RESPONSE TO ARGUMENT: Applicants argue: 1) the scope of chimeric proteins encompasses those comprising a non-mutant *Spiroplasma* DNA methyltransferase polypeptide and is not limited to those comprising mutant *Spiroplasma* DNA methyltransferase polypeptides and 2) because sequences of *Spiroplasma* DNA methyltransferase, LexA, and LacI polypeptides were known in the art at the time of the invention, it would not require undue experimentation to make and use the full scope of the claimed invention.

Applicant's argument is not found persuasive. In response to argument 1), as noted above, the examiner has not narrowly interpreted "*Spiroplasma* DNA methyltransferase" as encompassing only those mutant forms of a *Spiroplasma* DNA methyltransferase polypeptide. Instead, in view of the definition of "DNA methyltransferase" as provided in the specification at p. 13, lines 3-11, the examiner has interpreted *Spiroplasma* DNA methyltransferase polypeptide as encompassing mutant *and* non-mutant sequences that are capable of methylating DNA. However, it should be noted that, according to applicant's specification, it would appear that in order for the chimeric polypeptide to function as recited in claims, *i.e.,* the *Spiroplasma* DNA methyltransferase polypeptide specifically methylates CpG sites adjacent to a LexA binding region or a Lac operator sequence, it is necessary to mutate the *Spiroplasma* DNA methyltransferase in order to reduce its intrinsic DNA binding activity (see p. 39, lines 13-24 and p. 40, lines 1-8). As such, based on applicant's specification, it would

appear that mutation of the *Spiroplasma* DNA methyltransferase polypeptide is necessary in order that the chimeric protein "specifically methylates CpG sites" adjacent to a LexA binding region or a Lac operator sequence.

In response to argument 2), in view of applicant's disclosure that the *Spiroplasma* DNA methyltransferase moiety should be mutated in order that a chimeric protein have *specific* binding activity, a non-mutant *Spiroplasma* DNA methyltransferase polypeptide fused to a LexA protein or a LacI protein would not be encompassed by the scope of the claims.

It is the examiner's position that undue experimentation is required for a skilled artisan to make and/or use the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). MPEP 2164.04 states, "[w]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection" and that "[t]he language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or

that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims." Accordingly, the Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: According to the specification at p. 13, lines 3-11, a "DNA methyltransferase" is defined as encompassing mutant *and* non-mutant sequences that are capable of methylating DNA. As such, the examiner has broadly interpreted a *Spiroplasma* DNA methyltransferase polypeptide as encompassing any polypeptide that is capable of methylating DNA. Also, the specification at p. 18, lines 10-11 acknowledges that the chimeric protein can include a "mutated LexA DNA binding protein." Further, although not expressly stated in the specification, the examiner has interpreted a LacI protein as encompassing mutant LacI proteins. As noted above, the scope of the claims does not encompass any chimeric protein comprising a *Spiroplasma* DNA methyltransferase polypeptide and a LexA DNA binding protein or a LacI protein. Instead, the scope of the claims is limited to those that have the ability to *specifically* methylate CpG sites adjacent to a LexA binding region or a LacI operator sequence.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The amino acid sequence of a polypeptide determines said polypeptide's structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.*, expectedly

intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.,* multiple substitutions. At the time of the invention, methods for isolating or generating variants of a given polypeptide acid were known in the art. However, neither the specification nor the state of the art at the time of the invention provide the necessary guidance for altering a *Spiroplasma* DNA methyltransferase, LexA DNA binding protein, or a LacI protein with an expectation of obtaining a polypeptide having the ability to *specifically* methylate CpG sites adjacent to a LexA binding region or a LacI operator sequence. At the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity/utility. For example, Branden et al. (cited in the Office action mailed 3/17/2004) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). Applicant's own specification acknowledges this high level of unpredictability by noting that "[i]t cannot be predicted

as to which mutations might give the desired reduction in affinity for DNA" (p. 40, lines 10-11).

The amount of direction provided by the inventor and The existence of working examples: While the specification discloses the vectors pLS and pLM9, it is noted that these vectors encode a chimeric polypeptide comprising a non-mutant *Spiroplasma* DNA methyltransferase linked to a LexA DNA binding protein or a LacI protein, which, as noted above, does not appear to be encompassed by the scope of the claims. In this case, the specification fails to disclose even a single working example of a mutant *Spiroplasma* DNA methyltransferase linked to a LexA DNA binding protein or a LacI protein that has the desired activity of *specifically* methylating CpG sites adjacent to a LexA binding region or a LacI operator sequence. While the specification provides general guidance for altering the amino acid sequences of *Spiroplasma* DNA methyltransferase and optionally LexA DNA binding protein and/or LacI protein, a skilled artisan has no expectation that the resulting variants as encompassed by the claims will maintain the desired activity of *specifically* methylating CpG sites adjacent to a LexA binding region or a LacI operator sequence.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of isolating or generating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen – by a trial and error process – for all polypeptide variants and encoding nucleic acids having a substantial number of modifications as encompassed by the claims for those encoded polypeptides having the desired activity/utility, particularly as

the specification gives no expectation that the experimentation will actually achieve the desired chimeric protein and encoding nucleic acid.

In view of the breadth of the claims, the lack of even a single working example, the high level of unpredictability, and the amount of experimentation required, which may or may not result in the desired chimeric protein and encoding nucleic acid, undue experimentation is necessary for a skilled artisan to make the claimed invention.

Conclusion

[12] Status of the claims:

Claims 48-56 are pending.

Claims 48-56 are rejected.

No claim is in condition for allowance.

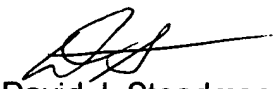
This is a continued examination of applicant's earlier Application No. 09/051,013. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Monday to Friday, 7:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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Primary Examiner
Art Unit 1656